## REMARKS

In the Office Action dated May 4, 2005, the Examiner indicated that claim 12 was allowed, claims 20 and 21 were objected to as depending on a rejected claim but were indicated allowable if rewritten in independent form, claims 1-11, 13-19 and 22-29 were rejected, and claims 30-109 were withdrawn from further consideration. The Examiner, however, indicated that the method claims 30-109 would be rejoined with the rejected compound claims when the compound claims were determined to be allowable. Accordingly, in response, Applicant has rewritten claims 20 and 21, and submits the following argument. In view of the above amendments and following remarks, reconsideration of the claims is requested.

As noted above, claim 12 was indicated as being allowed. Claims 20 and 21 were objected to as depending on a rejected claim, i.e. claim 17. The Examiner, however, indicated that claims 20 and 21 would be allowable if rewritten in independent form. Accordingly, Applicant has rewritten claim 20 in independent form and revised claim 21 to be dependent upon claim 20. Accordingly, Applicant believes claims 12, 20 and 21 are now all allowable.

In the Office Action, the Examiner rejected claims 1-11, 13-19 and 22-29 under the Doctrine of Obviousness Type Double Patenting as being unpatentable over claims 1-11 and 14-16 of U.S. Patent 5,843,928. The Examiner indicated that although the conflicting claims are not identical, they are not patentably distinct from each other since the presently claimed compounds are generically covered by the structure illustrated in U.S. Patent '928. Although none of the presently claimed compounds are specifically exemplified in the '928 patent, the Examiner indicated it would be obvious to one skilled in the art to prepare additional beneficial compounds because the '928 patent generically teaches such compounds. Applicant, however, disagrees with the Examiner's conclusions for the following reasons.

Applicant believes it would not have been obvious to select the presently claimed compounds from all of the compounds covered by the generic structure in the '928 patent

because of the differences in the biological activities of the presently claimed compounds versus those described in the '928 patent. More specifically, the biological activities of the presently claimed compounds can be found in the specification in Figures 5 and 6 which are described in paragraph 00163 on page 58 of the specification as filed. As stated therein:

> "Figures 5 and 6 show a comparison of the calcemic activity of the known active 19-nor analog 2MD and the presently claimed F-Wit, 1AGR and 1AGS analogs. Figure 5 shows that F-Wit, 1AGR and 1AGS all have relatively high intestinal calcium transport activity, and are more active than 2MD in intestinal calcium transport activity. Also, Figure 6 shows that F-Wit, 1AGR and 1AGS all have significant ability to mobilize calcium from bone, and are less active in this regard than 2MD. Thus, in summary, the 2-propylidene-19-nor-analogs of structure I, and particularly F-Wit, 1AGR and 1AGS, show a selective activity profile combining high potency in inducing the differentiation of malignant cells, relatively high intestinal calcium transport activity and moderate bone calcium mobilization activity."

Thus, the presently claimed 2-propylidene-19-nor-analogs in the present patent application all have intestinal calcium transport activity greater than 2MD (2-methylene-19-nor-20(S)-1$\alpha$,25-dihydroxyvitamin $D_3$). In addition, although the claimed 2-propylidene-19-nor-analogs have significant bone calcium mobilization activity, they are less active in this regard than 2MD.

Applicant believes the compound 2MD is the closest prior art compound disclosed in the '928 patent with regard to the presently claimed E and Z isomers of claims 15 and 16. The Examiner will note that there is only one difference between the compounds claimed in the present claims 15 and 16 and the analog 2MD. That difference lies in the fact that 2MD has a methylene group attached at the carbon 2 position whereas the E and Z isomers of present claims 15 and 16 have a hydroxypropylidene group attached at the 2-carbon position. Thus, there is only one structural difference between the compounds of claims 15 and 16 and the analog 2MD.

With regard to the E and Z isomers of compounds 13 and 14, Applicant believes the closest prior art compound is 2-methylene-19-nor-1α,25-dihydroxyvitamin $D_3$ which is also disclosed in the '928 patent. Again, the only difference between the E and Z isomers of present claims 13 and 14 and 2-methylene-19-nor-1α,25-dihydroxyvitamin $D_3$ is the hydroxypropylidene substitution at carbon 2. As the Examiner can see, the '928 compound has a methylene group attached at the carbon 2 position instead of a hydroxypropylidene group. Thus, once again, there is only one difference between the compounds of claims 13 and 14 and the compound 2-methylene-19-nor-1α,25-dihydroxyvitamin $D_3$ disclosed in the '928 patent.

The calcemic activities for the compounds 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin $D_3$ (referred to herein as 2MD) and 2-methylene-19-nor-1α,25-dihydroxyvitamin $D_3$ are set forth in U.S. Patent 5,843,928, particularly in Tables 1 and 2 found at columns 16 and 17 of the '928 patent. The '928 patent summarizes the calcemic activity of these two compounds beginning at column 15, line 61 and continuing through column 16, line 22 as follows:

> "Surprisingly, however, the 2-methylene substitutions produced highly selective analogs with their primary action on bone. When given for 7 days in a chronic mode, the most potent compound tested was the 2-methylene-19-nor-20S-1,25-$(OH)_2D_3$ (Table 1). When given at 130 pmol/day, its activity on bone calcium mobilization (serum calcium) was of the order of at least 10 and possible 100-1,000 times more than that of the native hormone. Under identical conditions, twice the dose of 1,25-$(OH)_2D_3$ gave a serum calcium value of 13.8 mg/100 ml of serum calcium at the 130 pmol dose. When given at 260 pmol/day, it produced the astounding value of 14 mg/100 ml of serum calcium at the expense of bone. To show its selectivity, this compound produced no significant change in intestinal calcium transport at either the 130 or 260 pmol dose, while 1,25-$(OH)_2D_3$ produced the expected elevation of intestinal calcium transport at the only dose tested, i.e. 260 pmol/day. The 2-methylene-19-nor-1,25-$(OH)_2D_3$ also had extremely strong bone calcium mobilization at both dose levels but also showed no intestinal calcium transport activity. The bone calcium mobilization activity of this compound is likely to be 10-100 times

> that of 1,25-$(OH)_2D_3$. These results illustrate that the 2-methylene and the 20S-2-methylene derivatives of 19-nor-1,25-$(OH)_2D_3$ are selective for the mobilization of calcium from bone. Table 2 illustrates the response of both intestine and serum calcium to a single large dose of the various compounds; again, supporting the conclusions derived from Table 1."

Thus, it can be concluded from the above statement and the data contained in the '928 patent that the 2-methylene compounds have little, if any, intestinal calcium transport activity but have very potent bone calcium mobilization activity at the doses tested, as compared to 1α,25-dihydroxyvitamin $D_3$.

A comparison of the 2-methylene analogs disclosed in the '928 patent and the hydroxypropylidene compounds of claims 13-16 in the present patent application shows that there are significant differences in the calcemic activities of these compounds. The 2-methylene analogs in the '928 patent have little, if any, intestinal calcium transport activity and extremely high bone calcium mobilization activity. In contrast, the presently claimed hydroxypropylidene compounds of claims 13-16 all have very high intestinal calcium transport activity, "and are more active than 2MD in intestinal calcium transport activity" as stated in the present patent application (paragraph 00163 quoted above). In addition, the presently claimed hydroxypropylidene compounds, although having significant ability to mobilize calcium from bone, "are less active in this regard than 2MD," as also stated in the present patent application (paragraph 00163 quoted above). Thus, the presently claimed hydroxypropylidene compounds have significantly different calcium transport activity as well as bone calcium mobilization activity than the 2-methylene analogs disclosed in the '928 patent. Clearly, such activities would not be predicted based upon the structural similarity of the two compounds. One skilled in the art would have predicted that the compounds should have approximately the same intestinal calcium transport activity and bone calcium mobilization activity due to their structural similarity, but instead, it is clear that the presently claimed hydroxypropylidene compounds have much higher intestinal calcium transport activity and slightly less bone calcium mobilization activity than the 2-methylene analogs disclosed in the '928 patent.

As a result, Applicant believes these properties are unexpected and provide a basis for unobviousness over the 2-methylene analogs disclosed in the '928 patent.

Accordingly, Applicant believes the Examiner should withdraw the obviousness type double patenting rejection based on the 2-methylene analogs disclosed in the '928 patent.

In the Office Action, claims 1-11, 13-19 and 22-29 were rejected under 35 USC §103(a) as being unpatentable over U.S. Patent 6,392,071. Again, the Examiner alleges that the hydroxypropylidene compounds claimed in the present application are obvious in view of the generic structure shown in the '071 patent and the fact that one of the substituents disclosed in the '071 patent is a hydroxyalkyl substituted on 2-methylene vitamin D compounds. Thus, the Examiner states that one skilled in the art would have been motivated to prepare additional compounds embraced by the genus of the '071 patent as the presently claimed compounds are suggested by the reference as a whole. Applicant, however, disagrees with the Examiner's conclusion for the following reasons.

The closest compounds taught in the '071 patent to the presently claimed hydroxypropylidene compounds of claims 13-14 is 2-methylene-19-nor-1α,25-dihydroxyvitamin $D_3$ and the closest compound taught in the '071 reference with respect to the hydroxypropylidene compounds of claims 15 and 16 is 2-methylene-19-nor-20(S)-1α,25-dihydroxyvitamin $D_3$ (the herein referred to 2MD compound). The 2-methylene compounds disclosed in the '071 reference are the closest compounds disclosed in the '071 patent because in each instance there is only one different substituent substitution. In other words, for the compounds claimed in claims 13-14, the only difference between these compounds and 2-methylene-19-nor-1α,25-dihydroxyvitamin $D_3$ is the fact that these compounds have a hydroxypropylidene group at the carbon 2 position whereas the '071 compounds have a methylene group at the carbon 2 position. Likewise, the only difference between the compounds of claims 15-16 and 2MD is that the compounds of claims 15-16 have a hydroxypropylidene substituent at carbon 2 and 2MD as a methylene group at carbon 2.

Previously in these remarks, Applicant has distinguished the compounds of claims 13-16 from the 2-methylene compounds based upon their different biological activities (see the arguments in the first half of these remarks). Thus, Applicant believes it has compared the biological activities of the closest compounds taught in the '071 patent with the claimed compounds of claims 13-16, and has indicated that such biological activities would not have been predicted based upon the structural similarity of the presently claimed compounds versus the 2-methylene compounds. The presently claimed compounds clearly have significantly different calcium transport and bone calcium mobilization activities than the 2-methylene analogs taught in the '071 reference. As previously stated, one skilled in the art would have predicted that the compounds should have approximately the same intestinal calcium transport and bone calcium mobilization activities due to their structural similarities, but instead, it is clear that the presently claimed hydroxypropylidene compounds have much higher intestinal calcium transport activity than the 2-methylene analogs. As a result, Applicant believes these properties are unexpected and provide a basis for unobviousness over the 2-methylene analogs, which are the closest compounds taught in the '071 reference.

The Examiner should note that the '071 reference also teaches vitamin D compounds having extended side chains at the 26 and 27 carbon positions. Applicant refers the Examiner to the side chains illustrated at column 4, lines 35-55 and to the compounds identified as numbers 35, 45, 46 and 47. However, each of these compounds are <u>not</u> the closest prior art compounds to those claimed in present claims 13-16. Each of those illustrated compounds has at least two differences between their structures and the presently claimed compounds whereas the 2-methylene analogs have only one difference, as previously noted herein. More specifically, compound 35 (the 26,27-dihomo compound) has a methylene group at carbon 2 as well as an extra methylene group at carbon 26 and an extra methylene group at carbon 27. The presently claimed compounds of compounds 15 and 16 have a hydroxypropylidene group at carbon 2 and only methyl

groups at carbons 26 and 27. Thus, there are three structural differences between compound 35 and the compounds of claims 15 and 16.

With regard to compound 45 (the 26,27-dimethylene-24-dehydro compound) illustrated in the '071 patent, this compound has a 5-membered ring structure at the 26,27 positions, a double bond between carbons 24 and 25 in the side chain, and has a methylene group attached at carbon 2. In contrast, the compounds of claims 15 and 16 have a hydroxypropylidene group at carbon 2 and only a methyl group at carbons 26 and 27. Once again, this indicates that there are at least three differences between compound 45 and the compounds of claims 15 and 16.

With regard to compound 46 (the 26,27 dimethylene-25-methoxy compound) illustrated in the '071 patent, this compound has a 5-membered ring attached at the 26,27 carbon positions, a methoxy group attached to carbon 25 and a methylene group attached to carbon 2. In contrast, the compounds of claims 15 and 16 have a hydroxypropylidene group attached to carbon 2, a hydroxy group attached to carbon 25 and methyl groups attached to carbons 26 and 27. Clearly, compound 46 appears to have at least four different structural substituents than the presently claimed hydroxypropylidene compounds of claims 15 and 16.

Finally, referring to compound 47 (the 26,27-dimethylene compound) illustrated in the '071 patent, this compound has a 5-membered ring structure attached at the 26,27 carbon positions and a methylene group attached at carbon 2. In contrast, the compounds of claims 15 and 16 have a hydroxypropylidene group attached at carbon 2 and methyl groups attached at carbons 26 and 27. Again, there are at least three different structural substituents for the compound 47 as compared to the hydroxypropylidene compounds of claims 15 and 16.

One can see that the compounds 35, 45, 46 and 47 are thus clearly not the closest prior art compounds to the hydroxypropylidene compounds claimed in claims 13-16 of the present patent application. The closest compounds are clearly the 2-methylene compounds disclosed in the '071 patent and the '928 patent. There is only one structural

difference between the 2-methylene compounds and the presently claimed hydroxypropylidene compounds whereas the compounds 35, 45, 46 and 47 of the '071 patent have in each case at least 3 or 4 different structural differences. Thus, Applicant believes it has compared the biological activities of the presently claimed compounds to the closest and most structurally similar compounds disclosed in the '928 and '071 patents. As previously noted herein, the presently claimed hydroxypropylidene compounds have significantly different calcium transport and bone calcium mobilization activities than the 2-methylene analogs. Clearly, such activities would not have been predicted based upon the structural similarity of these compounds. As a result, Applicant believes these properties are unexpected and provide a basis for unobviousness over the 2-methylene analogs taught in the '071 reference.

Accordingly, Applicant believes the Examiner should withdraw the obviousness rejection based upon the '071 reference.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,

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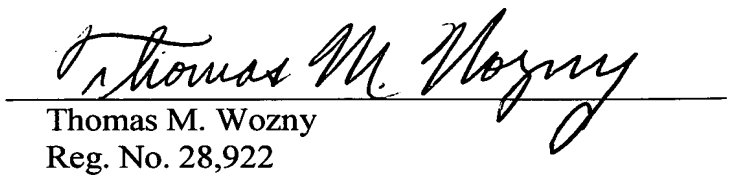
By 

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